

**REMARKS**

In the amendments reflected in the claim listing above, claims 22-27 have been amended to more particularly point out and distinctly claim the subject matter Applicants regard as their invention. Claims 28-33 are new. Support for the amendments can be found throughout the specification. Now pending in this application are claims 22-33. No new matter has been added.

The amendments to the claims are being made for the purpose of expediting prosecution and are made without prejudice or waiver. Applicants reserve the right to present the original claims in this or a continuing application.

**The Office Action**

The claims stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner states that the pending claims do not find support in certain application(s) to which this application claims priority. This rejection is traversed.

Even if the Examiner's position regarding the priority claim is correct, the claims should not be rejected under 35 U.S.C. § 112, first paragraph. Applicants contend that the present claims are fully supported for purposes of written description and enablement in the presently-pending application as filed, and therefore cannot be rejected under 35 U.S.C. § 112, first paragraph. If the Examiner's position is correct, then perhaps certain of the present claims would not be entitled to the filing date of certain application(s) to which this application claims priority, but the Examiner makes the argument only in the context of applying certain alleged prior art for rejecting the claims (although, as discussed further

Peter Meltzer, *et al.*  
U.S.S.N. 09/975,586  
Page 8 of 12

below, the pending claims patentably distinguish over the references cited by the Examiner).

Applicants respectfully submit that the rejection under 35 U.S.C. § 112, first paragraph, is improper and should be withdrawn.

Claims 22, 23, and 27 stand rejected under 35 U.S.C. § 102(e) as anticipated by Kuhar (U.S. Patent No. 6,358,492; “Kuhar ‘492”). This rejection is traversed.

Even if the Kuhar ‘492 reference is prior art to the pending claims, Kuhar clearly does not anticipate the claims as amended. The Kuhar ‘492 reference discloses certain 3 $\alpha$  tropane analogs in which the ring system is substituted at the 2 position with a methyl ester (a methoxy carbonyl group). The pending claims (as amended) are directed to compounds in which the 2 position is substituted with an alkylcarbonyl or carbamoyl group. The claimed compounds are not taught nor suggested by the Kuhar ‘492 reference. Applicants therefore urge that the Kuhar ‘492 reference cannot anticipate the pending claims.

Reconsideration and withdrawal of this rejection is therefore proper and the same is requested.

Claims 22-27 stand rejected under 35 U.S.C. § 103 as unpatentable over Clarke (US 3,813,404), Kuhar (US 5,496,953, hereinafter “Kuhar ‘953”), and Davies (US 6,008,227) in view of Kuhar (US 6,358,492). This rejection is traversed.

Even if the Kuhar ‘492 reference is a § 102 reference with respect to the pending claims, the cited references whether alone or in combination, do not teach or suggest the compounds of the pending claims.

The teachings of the Kuhar '492 reference have been described above. The Clarke reference discloses certain tropane compounds in which the bicyclic ring system is substituted at the 2 position with an alkyl ester (a methoxy carbonyl group). These compounds do not include the compounds of this invention as presently claimed, in which the compounds are substituted at the 2 position with an alkylcarbonyl or carbamoyl group. Furthermore, as the Examiner has recognized, the Clarke reference also does not disclose tropane analogs in which the bicyclic ring system is substituted at the 3 position with a substituent in the alpha orientation, as required by the pending claims. Although the Examiner has stated that the Clarke reference teaches "that any stereochemical arrangement of the nucleus and substituent groups is contemplated," this statement does not establish that the Clarke reference contains an enabling teaching or suggestion of compounds in which the substituent at the 3 position is in the alpha configuration, as in the presently-claimed compounds. Applicants therefore contend that the Clarke reference, alone or in combination with the other references cited by the Examiner, cannot teach or suggest the presently-claimed compounds.

The Kuhar '953 reference discloses tropane analogs in which, as the Examiner has recognized, the bicyclic ring system is substituted at the 3 position with a substituent in the beta orientation (not the alpha orientation as required by the pending claims). In addition, the Kuhar '953 reference does not disclose any compounds in which the bicyclic ring system is substituted at the 2 position with an alkylcarbonyl or N-(O-alkyl) carbamoyl group (except the compound RTI-186), as required by the pending claims. Applicants therefore contend that the Kuhar '953 reference, alone or in combination with the other references cited by the Examiner, cannot teach or suggest the presently-claimed compounds.

Peter Meltzer, *et al.*  
U.S.S.N. 09/975,586  
Page 10 of 12

The Davies reference discloses tropane analogs in which, as the Examiner has recognized, the bicyclic ring system is substituted at the 3 position with a substituent in the beta orientation (not the alpha orientation as required by the pending claims). Applicants therefore contend that the Davies reference, alone or in combination with the other references cited by the Examiner, cannot teach or suggest the presently-claimed compounds.

The Examiner then states that the Kuhar '492 reference:

teaches that 3-alpha isomers of several 3-beta (substituted phenyl) tropanes exhibit selectivity for dopamine transporter [sic] since their affinity for serotonin transporter is reduced . . . one skilled in the art would have been motivated to prepare the instant selective dopamine ligands (3-alpha isomers of tropine derivatives) by modifying non-selective dopamine and serotonin ligands (3-beta isomers of tropine derivatives) of Clarke, Kuhar and Davies since Kuhar teaches the selectivity of 3-alpha isomers for dopamine transporter over 3-beta isomers.

Office Action of January 23, 2004 at paragraph 9.

This rejection is traversed. Applicants respectfully point out that, as described in the MPEP at 2144.09, "isomerism involve[s] close structural similarity which must be considered with all other relevant facts in determining the issue of obviousness"; that is, the mere fact that two compounds appear similar does not automatically result in *prima facie* obviousness. Instead, "the claimed invention and the prior art must each be viewed 'as a whole'". MPEP 2144.09 (citations omitted). In the present case, it is clear from the teachings of the cited references and the present specification that relatively small structural changes in tropine compounds (such as the use of unnatural stereoisomers) can result in significant differences in binding activity.

Indeed, while the Examiner has pointed to the Kuhar '492 reference as teaching that the 3-alpha compounds of that reference are more selective for the dopamine transporter than the 3-beta compounds, the Kuhar '492 reference also teaches that the 3-alpha compounds are less potent than the corresponding 3-beta compounds (see, e.g., Kuhar '492 at column 2, lines 1-4).

Applicants contend that, prior to the present invention and absent the teachings of the present specification, one of ordinary skill in the art would not have been motivated to modify the teachings of the cited references as suggested by the Examiner to arrive at the claimed invention, nor would there have been a reasonable expectation that such modifications would be successful. As the Court of Appeals for the Federal Circuit (CAFC) has stated, an Examiner "cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." See, e.g., *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1780, 1783 (Fed. Cir. 1988).

In the present case, the Examiner has chosen certain isolated features from a variety of references and attempted to combine them to arrive at the claimed invention by using the present disclosure as a blueprint. This is not the correct analysis; as the MPEP states, the teachings of the prior art must be considered as a whole. Applicants submit that a *prima facie* case of obviousness cannot be made in this instance, when the teachings of the prior art as a whole are considered.

Reconsideration and withdrawal of the rejection is proper and the same is requested.

Peter Meltzer, *et al.*  
U.S.S.N. 09/975,586  
Page 12 of 12

## CONCLUSION

It is respectfully submitted that the present application is in condition for allowance. An early consideration and notice of allowance are earnestly solicited.

Applicants believe that additional fees are not required to complete the filing requirements for the subject application or otherwise in connection with this submission. However, if a fee is required, a fee paid is inadequate or credit is owed for any excess fee paid, you are hereby authorized and requested to charge/credit Deposit Account No. **04-1105**.

Respectfully submitted,



Date: March 14, 2005  
Customer No.: 21874

---

Mark D. Russett, Reg No. 41,281  
Gregory B. Butler, Reg. No. 34,558  
EDWARDS & ANGELL, LLP  
P.O. Box 55874  
Boston, MA 02205  
Tel: (617) 439-4444